Introduction

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‘Taking X-ray phase contrast imaging into mainstream applications’ and its satellite workshop ‘Real and reciprocal space X-ray imaging’

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A double event, supported as part of the Royal Society scientific meetings, was organized in February 2013 in London and at Chicheley Hall in Buckinghamshire by Dr A. Olivo and Prof. I. Robinson. The theme that joined the two events was the use of X-ray phase in novel imaging approaches, as opposed to conventional methods based on X-ray attenuation. The event in London, led by Olivo, addressed the main roadblocks that X-ray phase contrast imaging (XPCI) is encountering in terms of commercial translation, for clinical and industrial applications. The main driver behind this is the development of new approaches that enable XPCI, traditionally a synchrotron method, to be performed with conventional laboratory sources, thus opening the way to its deployment in clinics and industrial applications. The satellite meeting at Chicheley Hall, led by Robinson, focused on the new scientific developments that have recently emerged at specialized facilities such as third-generation synchrotrons and free-electron lasers, which enable the direct measurement of the phase shift induced by a sample from intensity measurements, typically in the far field. The two events were therefore highly complementary, in terms of covering both the more applied/translational and the blue-sky aspects of the use of phase in X-ray research.

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1. X-ray phase contrast imaging

Since Roentgen’s discovery well over a century ago, X-ray imaging has been based on attenuation. While this is an effective and reliable approach, it is known to have limitations whenever objects with similar attenuation characteristics have to be distinguished, as this leads to poor image contrast. One possible solution is to generate image contrast by exploiting phase changes in the X-ray wavefront rather than attenuation: this approach is called X-ray phase contrast imaging (XPCI). Its main advantage is that the term responsible for phase effects (the unit decrement of the real part of the refractive index) is much larger than the imaginary part, responsible for attenuation. In many practical cases, this difference can be up to 1000-fold. Hence, albeit that it can be difficult to detect, phase is intrinsically a much stronger effect and can therefore lead to much higher image contrast if appropriately exploited.

The first X-ray phase contrast image dates back to 1965 and was acquired by Bonse & Hart [1] with a crystal interferometer, which has been bearing their names since. We were fortunate enough to have Prof. Hart attending our conference. Following a significant attempt by Ando & Hosoya [2] in 1972, the idea of using a crystal-based X-ray interferometer was picked up again in the 1990s, in particular by Momose’s group. XPCI exploded in the mid-1990s, and, to the best of our knowledge, the first of a long series of papers published from 1995 onwards is Momose’s [3], published on 1 January 1995, on results already presented in the previous year. Momose and his group continued to explore medical and biological applications of XPCI implemented with the Bonse–Hart interferometer, as reported, for example, in their 1996 Nature Medicine paper [4].

Almost simultaneously, researchers started to explore a different approach to the use of crystals in XPCI—namely the use of a perfect crystal as an ‘angular analyser’. It was in fact observed that the faint distortions in the wavefront caused by phase changes translate directly into slight changes in the X-ray direction (X-ray refraction), which could therefore be picked up by a system with sufficient angular sensitivity like a perfect crystal. The fact that the refraction angle is proportional to the gradient of the phase shift gave rise to the name ‘differential’ XPCI, which is common to other methods listed below, such as edge-illumination and Talbot interferometry. The most famous paper pioneering this approach is the 1995 Nature letter by Davis et al. [5]. It has to be said, however, that a few known examples exist that pre-date that deservedly famous paper, where effectively the same method had been used to address specific problems, and the results were published in journals with relatively limited diffusion [6,7]. Another paper on the crystal method appeared later in the same year [8] and the method continued to be explored later, leading to some of the first simplified phase retrieval algorithms [9] and extraction of the first quantitative X-ray ‘dark-field’ images [10–12] (qualitative dark-field images had already been presented in [5]).

Still in 1995, a much simpler implementation, based on free-space propagation, was proposed by Snigirev et al. [13]. Through this approach, phase contrast images are acquired without the need for any additional optical element, simply by increasing the distance between sample and detector. If the source possesses enough coherence, this is sufficient to detect phase-induced interference fringes at the boundaries of the imaged objects. In the following year, Wilkins et al. [14] demonstrated that this approach works also with polychromatic radiation, something that was impossible to observe before as the use of a crystal automatically renders the beam monochromatic. Interestingly, similar images had been obtained before, but the substantially improved image contrast had not been interpreted on the basis of phase effects (e.g. [15]). Owing to its simplicity of implementation, the free-space propagation technique is still widely used, and it is the only one to date to have reached the in vivo stage for human patients [16].

A method that combines the angular selectivity principle exploited with crystal ‘analysers’ and the simplicity of free-space propagation, called edge-illumination XPCI, was developed in the late 1990s [17]. As the name suggests, it performs a fine selection on X-ray direction by illuminating only the physical edge of the detector pixels, and by doing so it eliminates the need for a perfect crystal, opening the way to polychromatic and divergent X-ray beams. This was later exploited...
to adapt the method for use with conventional X-ray sources [18], which also led to the first quantitative phase retrieval performed with incoherent illumination of the sample [19].

In the early 2000s, a further approach was introduced, based on the adaptation to X-rays of Talbot and Talbot–Lau interferometers, well-known methods among the optics community. This adaptation was made possible by novel nanofabrication techniques, which enabled the development of gratings with a pitch sufficiently small to produce Talbot ‘self-images’ [20] at X-ray wavelengths when coherently illuminated. The approach was first demonstrated in the ‘Talbot’ set-up by David et al. [21] and by Momose’s group shortly afterwards [22]; a few years later, Pfeiffer et al. [23] demonstrated that the Talbot–Lau arrangement could also be implemented with X-rays, opening the way to the use of laboratory sources. In a further study, it was shown that the same set-up could also be used to obtain quantitative dark-field images [24], along the lines of what was previously done with analyser crystals [10–12]. To extract phase and dark-field signals, a technique called phase stepping is employed, in which one of the two (Talbot) or three (Talbot–Lau) gratings is scanned with respect to the others, and individual images are acquired at each scanning position. Later on, Wen et al. [25] developed a similar approach, which, however, employed a single grating, and, instead of using a phase-stepping method to isolate the different signals, did so by applying a Fourier-based analysis method to a single frame.

Quite remarkably, most of the leading figures behind the above developments agreed to participate in the conference, which meant that most of the above topics were covered in the various talks. Another interesting aspect that emerged is that the field is continuing to evolve, with new examples of implementation already being presented at this same meeting (e.g. Wen et al. [26] realized gratings with nanometric pitch which led to a hybrid between Talbot and Bonse–Hart interferometry), new implementation schemes (e.g. [27]), use of materials as common as paper to replace gratings or analysers [28] and much more. This extreme liveliness indicates a prosperous future for the area, both in terms of new methods and new applications, and definitely looks encouraging in terms of ultimately reaching the ‘translation into mainstream application’ goal which inspired this meeting.

2. Taking X-ray phase contrast imaging into mainstream applications

The meeting started on 11 February 2013 at 09.00. The first session was chaired by Dr Alessandro Olivo, and featured talks from some of the pioneers in the area. After a brief introduction by the chairman, which summarized some of the key steps in the evolution of phase contrast methods, the first talk (‘On the genesis of XPCI—free-space propagation and other implementations’) was very appropriately given by Dr Steve Wilkins from the Commonwealth Scientific and Industrial Research Organization, one of the key pioneers in the area and author of some of the early landmark papers. Dr Wilkins gave an historical introduction and discussed how free-space propagation led to many other interesting approaches. The second talk (‘Development and recent applications of grating-based X-ray phase contrast for biomedical imaging’) was given by Prof. Franz Pfeiffer of Technischen Universität München, who discussed his pioneering developments in grating-based methods. The following speaker was Atsushi Momose from Tohoku University, Japan, who discussed both his early research on Bonse–Hart interferometers and his more recent interest in Talbot–Lau interferometry. He concluded his presentation by discussing the development of a prototype system capable of imaging human joints in vivo (hence the talk’s title ‘X-ray phase imaging—from synchrotron to hospital’). The session was closed by Dr Zhong Zhong from the Brookhaven National Laboratory, one of the pioneers in analyser-based methods, who discussed these in detail in his talk ‘Crystal-based methods: from synchrotron to X-ray tube’.

The second session, chaired by Dr Alberto Bravin from the European Synchrotron Radiation Facility in France, was focused on applications. It was opened by a talk on arguably one of the most noteworthy applications currently underway—the in vivo mammography programme at the Trieste synchrotron ELETTRA. The talk (‘Clinical XPCI-based mammography with synchrotron radiation’) was given jointly by a radiologist (Dr Maura Tonutti from the Cattinara Hospital in
Trieste) and a physicist (Prof. Renata Longo from the University of Trieste), both having a leading role in the above programme, which enabled an appreciation of both perspectives of the problem. This was followed by a talk from Prof. Marco Stampsanoni (Swiss Light Source/Eidgenössische Technische Hochschule), who discussed the possibility to adapt phase contrast mammography to conventional X-ray sources using grating interferometry in his talk ‘Phase contrast X-ray imaging in the clinic: a first mammography study’. The third talk (‘Boosting phase contrast with a two-arm interferometer using submicron grating periods’) was given by Dr Han Wen from the National Institutes of Health in Bethesda (MA, USA), who talked about possible medical and biological applications of an enhanced approach to grating interferometry obtained through substantially reducing the gratings’ pitch. The session was concluded by Dr Peter Munro from the University of Western Australia, who talked about the edge-illumination approach and discussed how the method’s flexibility enables different system designs that can be readily adapted by different applications, as summarized by the talk’s title (‘Medicine, material science and security: the versatility of the coded-aperture approach’).

The first session of the second day was chaired by Prof. Ian Robinson and was dedicated to new developments in X-ray source technology and their possible role in improving phase contrast imaging approaches. The session was opened by Dr Joe Ferrara from the US headquarters of RIGAKU in Woodland, TX, USA, who discussed the enhanced level of performance that can be reached through state-of-the-art rotating anode X-ray sources in his talk entitled ‘Rotating anode X-ray sources and their applications’. The second talk (‘Liquid-metal-jet sources for high-resolution phase-contrast bio-imaging’) was given by Prof. Hans Hertz from the KTH Royal Institute of Technology in Sweden, who presented a new technology which replaces the conventional anode in an X-ray tube with a liquid jet, enabling the concentration of higher powers on smaller focal spots. The session was concluded by Prof. Zulfikar Najmudin from Imperial College London, who reviewed the vast and rapidly growing area of plasma-based X-ray sources in his talk entitled ‘Phase contrast imaging with compact plasma based accelerators’, providing also examples of X-ray images acquired in his laboratory with one of these sources. This session only featured three talks as it was followed by a lively poster session, in which more than 30 posters were presented—some highlights from which have been included as short papers in this Discussion Meeting Issue.

The London part of the meeting was concluded by a session on industrial applications chaired by Prof. Phil Withers from the University of Manchester. The first speaker was Dr Ewald Roessl from the Philips Research Labs in Hamburg, who talked about the design of a prototype for scanning-based grating interferometry of the breast in his talk entitled ‘Clinical boundary conditions for differential phase contrast mammography’. The industrial focus meant that he took into account practical problems related to, for example, patient positioning as well as physical ones, for example phase sensitivity. The second talk (‘Phase demodulation methods for two-dimensional grating based X-ray interferometry’) by Kentaro Nagai from the Canon headquarters in Japan looked at practical solutions that could enable the quantitative separation of phase and absorption in two dimensions simultaneously without imposing an excessive burden on exposure times, again a key aspect in industrial applications. Unfortunately, the third speaker (Dr Rainer Raupach from Siemens) was unable to attend the meeting, so Nagai’s talk was followed by what was originally planned as the fourth talk of the session, i.e. ‘Investigation of the application of phase contrast imaging using a point X-ray source to industrial non-destructive testing (NDT)’, given jointly by Dr Kazuaki Suzuki and Dr Ian Haig from the UK branch of Nikon Metrology in Tring (Hertfordshire). Dr Haig briefly summarized the history of X-Tek, the company in Tring that became part of Nikon Metrology UK, and listed some of its pioneering developments in X-ray source technology, while Dr Suzuki provided some examples of the application of free-space propagation XPCI to non-destructive testing. The meeting was concluded by Prof. Ian Robinson, who gave a brief introduction to the topics of the satellite workshop ‘Real and reciprocal space X-ray imaging’, by introducing reciprocal space approaches, such as coherent diffractive imaging and X-ray ptychography, and providing some examples of applications currently under investigation in his group. This concluded
the meeting at the expected time (17.00) on Tuesday 12 February 2013. Most credit for the organization and smooth running of the meeting goes to Rose Cooper-Thorne, who has all our gratitude.

3. Real and reciprocal space X-ray imaging

A satellite meeting was organized by Prof. Ian Robinson and Dr Alessandro Olivo of University College London under the title of ‘Real and reciprocal space X-ray imaging’. It followed immediately from the London meeting, starting at 09.00 on Wednesday 13 February 2013 and ending at 17.00 on Thursday 14 February 2013. The meeting was held at the Royal Society’s Chicheley Hall, home of the Kavli Royal Society International Centre, Buckinghamshire, UK. The 2-day workshop was more oriented towards X-ray imaging methods than the translation to market. The programme focused on issues of complementarity between real-space methods (tomography and X-ray microscopy) and reciprocal space methods (such as coherent diffractive imaging and ptychography). The newest method discussed, X-ray ptychography, is actually a real/reciprocal space hybrid: it combines coherent diffraction patterns collected at every position of a scanning ‘probe’ to significantly boost the resolution of the final image which combines inversions of these reciprocal space diffraction patterns with the real-space pattern of the scanned array of sampled positions. The diffraction phase problem is solved along the way by self-consistency of the overlap regions between the probe positions.

The opening session on X-ray microscopy was chaired by Dr Janos Kirz of the Advanced Light Source, Berkeley who gave a general introduction to some of the methods he developed in the early years at Brookhaven’s synchrotron, the National Synchrotron Light Source. The first lecture was given by Dr Gerd Schneider of the Helmholtz-Zentrum Berlin, Germany on ‘Nanoscale X-ray imaging at Helmholtz-Zentrum Berlin’, in which new results of frozen cell imaging were presented in which phospholipid bilayers could be resolved. Dr Wataru Yashiro of Tohoku University, Japan then talked about ‘X-ray phase microscopy with gratings’, describing the Talbot effect and how it could be employed for phase contrast. This was followed by Prof. Chris Jacobsen of Argonne National Laboratory and Northwestern University with a talk on ‘Cold and in color: combining ptychography with fluorescence in a cryogenic microscope’, which described a new instrument he had designed with robotic sample changers for cryo-cooled samples. Lastly, Prof. John Spence of Arizona State University and Lawrence Berkeley Laboratory presented ‘Femtosecond X-ray lasers for imaging atomic structure and dynamics’ including a lot of information about how structure can be extracted from single X-ray ‘still’ snapshots.

The second session was on coherent diffraction imaging, introduced by Prof. Christoph Rau, from the Diamond Light Source, who described his new ‘Coherence and Imaging’ twin beamlines. Prof. Harry Quiney from the University of Melbourne, Australia, gave the first talk on ‘Partial coherence and structural disorder in diffractive X-ray imaging’ in which he described X-ray laser-induced electronic ordering of C60 crystals. Then, Dr Stefano Marchesini of Lawrence Berkeley National Laboratory talked about ‘Multiscale algorithms for mesoscale diffractive imaging’ in which he described the mathematical limitations of current algorithms and how they might be improved. Dr Stephan Hruszkewycz of Argonne National Laboratory then talked about ‘Bragg projection ptychography of nanostructured thin films’ in which he presented careful simulations of the effective ‘probe’ function that should be used when the focused beam divergence is greater than the rocking curve width of the crystalline sample. This was followed by drinks and a poster session with lively discussions. Some of the poster presenters chose to participate in a ‘rapid-fire’ oral presentation of a single summary slide of their work, which advertised the work that was being presented.

The second day started with a session on X-ray tomography, chaired by Prof. Robert Speller of University College London, who introduced some of the challenges of image interpretation in a medical context. Prof. Paola Coan of the Ludwig Maximilian University München addressed the question ‘Is phase contrast tomography of realistic human specimens feasible at clinically compatible doses?’ This was followed by Prof. Marco Stampanoni, from ETH Zurich and
Paul Scherrer Institut in Switzerland, who spoke about ‘Cutting-edge 4D imaging of dynamic phenomena at the Swiss Light Source’ with an impressively large number of images obtained from his beamline. Then, Dr Peter Cloetens from the European Synchrotron Radiation Facility in France talked about ‘Multi-modal 3D imaging of materials’ in which a series of images taken at different distances could be combined to yield precise phase contrast maps of high quality. Dr Robert Bradley from the University of Manchester ended the session with a talk about ‘Utilising laboratory X-ray phase contrast for research across disciplines’.

The last session was devoted to X-ray ptychography, introduced by Prof. Franz Pfeiffer of the Technischen Universität München, who was one of the first users of the new method with X-rays. The first speaker was Prof. John Rodenburg of the University of Sheffield, who reminisced about the early days of the method and talked about ‘Strengths and weaknesses of visible-light and electron ptychography’. Then Dr Ian McNulty, of Argonne National Laboratory, showed his results on ‘Ptychographic imaging of magnetic domains’ in which domain walls could be observed moving in an applied magnetic field. Dr Manuel Guizar-Sicairos from the Paul Scherrer Institut, Switzerland, then explained how ‘Signal-to-noise ratio and maximum likelihood principles applied to ptychography’, whereby significant improvements could be obtained. At the very end of the meeting, Dr Pierre Thibault from the Technical University of Munich gave a talk on ‘X-ray ptychography’ in which he explained that additional information could be extracted for fluctuating samples.

These speakers were all very positive about the future prospects of both real and reciprocal space imaging. They inspired considerable discussion during the workshop breaks and meals shared by all participants. These breaks and all facilities in Chicheley Hall were superbly organized by Tracey Wheeler, who deserves much credit for the successful outcome of the event.

References


